Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015;373:1095-105. DOI: 10.1056/NEJMoa1506459

(PDF updated September 30, 2015.)

SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to give readers additional information about their work.

Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho M-P, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, Teschler H. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure.

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SERVE-HF Study Centers and Investigators

The following is a list of centers that participated in the SERVE-HF study. Each center included at least two sites (i.e. cardiology clinic and sleep laboratory).

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Royal Adelaide Hospital	Dr. A Yeo	Adelaide	Australia
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Cardiocentro Ticino	Prof. T Moccetti	Lugano	Switzerland
Ospedale Regionale di Lugano	Prof. M Pons	Lugano	Switzerland
ST. Anne´s University Hospital	Dr. T Kara	Brno	Czech Republic
Ambulantes Cardiovasculäres Centrum Ravensburg	Dr. K Schlotterbeck	Ravensburg	Germany
Ambulantes Herzzentrum Kassel	Dr. A Utech	Kassel	Germany
Ärztezentrum Holthausen-Biene	Dr. L Stauff	Lingen	Germany
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Evangelisches Krankenhaus	Prof. E Vester	Düsseldorf	Germany
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Fachkrankenhaus Coswig	Prof. G Höffken	Coswig	Germany
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Herzzentrum Universität Dresden	Prof. R Strasser	Dresden	Germany
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Kardiologie Praxis Dr. Bonnekamp	Dr. Bonnekamp	Essen	Germany
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Kardiologische Praxis Dr. Burkhard-Meier	Dr. C Burkhard-Meier	Viersen	Germany
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Praxis Dr. Ebeling	Dr. O Ebeling	Schönefeld/ OT Waltersdorf	Germany
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Praxis Dr. Schnabel	Dr. A Schnabel	Meißen	Germany
Praxis Dr. Stratmann	Dr. M Stratmann	Dortmund	Germany
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Universitätsklinikum Mannheim	Dr. J Maurer	Mannheim	Germany
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Centre Hospitalier de Béziers	Dr. F Goutorbe, Dr. P Berdague	Beziers Cedex	France
Centre Hospitalier de Cannes	Dr. C Perrin, Dr. A Talbodec	Cannes Cedex	France
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CH Rene Dubos	Prof. P Jourdain, Dr. A Simo, Dr. F Funck	Pontoise	France
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CHR Metz, Hôpital de Bon-Secours	Dr. I Olaru, Dr. M Boursier	Metz	France
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CHU Bordeaux, Hopital Pellegrin	Prof. P Philip	Bordeaux Cedex	France
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CHU de Saint-Etienne, Hopital Nord	Dr. F Roche, Dr. I Court-Fortune	Saint-Etienne Cedex 2	France
CHU Grenoble, Hopital Michallon	Prof. P Levy, Dr. Y Neuder	Grenoble cedex 9	France
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CHU Lille, Hopital Cardiologique	Dr. P DeGroote	Lille Cedex	France
CHU Tenon	Dr. C Philippe	Paris cedex 20	France
CHU Toulouse, Hopital de Rangueil	Prof. A Pathak	Toulouse cedex	France
CHU Toulouse, Hopital Larrey	Dr. S Pontier	Toulouse cedex 9	France
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Clinique du Tondu	Dr. O Coste	Bordeaux	France
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Hopital Henri Mondor	Prof. L Hittinger, Dr. L Boyer	Creteil	France
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Castle Hill Hospital	Prof. A Clark	Cottingham	United Kingdom
Chesterfield Royal Hospital	Dr. J Cooke	Chesterfield	United Kingdom
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Patient inclusion criteria

Patients were eligible for inclusion in the SERVE-HF trial if they met the following inclusion criteria:

- Age ≥22 years;
- Chronic heart failure (HF) (defined as ≥12 weeks since diagnosis) according to current European Society of Cardiology guidelines;
- Left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF]) ≤45% determined using echocardiography, radionuclide angiography, left ventriculography or cardiac magnetic resonance imaging) documented <12 weeks before randomization;
- New York Heart Association (NYHA) class III or IV, or NYHA class II with ≥1 hospitalization for HF in the last 24 months;
- No hospitalization for HF in the 4 weeks prior to enrolment;
- Treatment with optimized medical treatment according to applicable guidelines with no new class of disease-modifying drug for ≥4 weeks prior to randomization (where there was no treatment with β-blockers or ACE inhibitors/angiotensin receptor blockers then the reasons must be documented);
- Predominant central sleep apnea (CSA) was defined as an apnea-hypopnea index (AHI) >15/h with ≥50% central events and a central AHI ≥10/h, derived from polygraphy (PG) or polysomnography (PSG) and based on total recording time, documented within 4 weeks of randomization, with flow measurement performed using a nasal cannula.

Patient exclusion criteria

Patients with any of the following were excluded from the SERVE-HF trial:

- Significant chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV_1) <50% of predicted (European Respiratory Society criteria) in the 4 weeks before randomization;
- Oxygen saturation ≤90% at rest during the day;
- Current use of positive airway pressure (PAP) therapy;
- Life expectancy <1 year for diseases unrelated to chronic HF;
- Cardiac surgery, percutaneous coronary intervention, myocardial infarction or unstable angina within the previous 6 months;
- Cardiac resynchronization therapy implantation scheduled or performed within 6 months prior to randomization;
- Transient ischemic attack or stroke within the previous 3 months;
- Primary hemodynamically-significant uncorrected valvular heart disease (obstructive or regurgitant) or any valvular disease expected to require surgery during the trial;
- Acute myocarditis/pericarditis within the previous 6 months;
- Untreated or therapy-refractory restless legs syndrome;
- Contraindication to the use of AutoSet CS2 because of symptomatic hypotension or significant intravascular volume depletion or pneumothorax or pneumomediastinum;

- Pregnancy.

Sleep apnea diagnosis and follow-up

The diagnosis of sleep apnea followed national clinical practice for each country participating in the study. Therefore, patients in France, UK, Sweden, Norway, Denmark were diagnosed by PG, while PSG was used in Germany.

A training program was initiated at the beginning of the study and a scoring guide was given to each study center. In addition, a qualification process was implemented. Each center needed to successfully score at least 3 PG recordings that were sent to a core lab to qualify for participation in the trial. Also, three local recordings had to be send to the core lab for quality control of the signals in order to qualify for participation in the trial.

Database for the current analysis

On March 26th, 2015 a meeting of the end point review committee (ERC) of SERVE-HF took place at which the 651st primary end point was adjudicated. The trial was immediately stopped with March 31st as effective date. The statistician performed a preliminary analysis of the primary end point and its components with the preliminary primary end point database (PEDBL) of March 26th and shared this information with the SERVE-HF Steering Committee. It was immediately clear that the primary study end point result was neutral and that there was an unexpected increase in cardiovascular mortality in patients allocated to adaptive servo-ventilation (ASV), which was promptly disclosed to the relevant authorities by the device manufacturer, ResMed. Since patients still in the study may have had their last study visit up to 12

months previously, centers were asked to contact their study patients to enable rapid collection of data on events that may have occurred up to the date of trial termination (final assessment). The final database was locked at July 17th. This database was used for the analyses presented here. However, the manuscript does not include an analysis of shocks in patients with an implanted cardioverter defibrillator (ICD) because these still have to be downloaded from the ICD devices and adjudicated for appropriateness, or data readouts from the ASV devices which require additional data cleaning and statistical modeling.

Hierarchical primary end point

The primary study end point was time to a first event of the composite of all-cause death, a life-saving cardiovascular intervention, or an unplanned hospitalization for worsening chronic heart failure as assessed by the ERC. Life-saving cardiovascular intervention, which was defined as being equivalent to death, included cardiac transplantation, long-term ventricular assist device implantation, resuscitation of sudden cardiac arrest, or appropriate shock for ventricular arrhythmia in patients with implantable cardioverter-defibrillators.

Subsequent hierarchical end points to be tested if the null hypothesis for the primary end point was rejected were the first secondary end point (as for the primary end point, but including cardiovascular death instead of all-cause death) and the second secondary end point (as for the primary end point, but including all-cause rather than heart failure-related unplanned hospitalization). Additional secondary end points were time to all-cause or cardiovascular death, change in NYHA class, and change in six-minute walk distance.

The closed testing procedure of Lehmacher et al. was used.[1] As such, if the null hypothesis for the primary end point (all-cause mortality or unplanned hospitalization for worsening HF) was not rejected, then testing ceased. As a result, no statistical analysis was conducted for the first and second secondary endpoints.

Definition of end point components

Hospitalization: admission to hospital requiring an overnight stay or resulting in death, including any prolongation of a hospitalization based on another serious event.

Unplanned hospitalization for worsening HF: unplanned hospitalization necessitated by HF and primarily for its treatment or when HF became a major component of the patient's hospital admission. A patient admitted for this reason had to show signs and symptoms of worsening HF and require treatment with oral or intravenous diuretics. Evidence of worsening HF had to include at least one of the following: increasing dyspnea on exertion, orthopnea, nocturnal dyspnea, pulmonary edema, increasing peripheral edema, increasing fatigue or decreasing exercise tolerance, renal hypoperfusion (i.e. worsening renal function), raised jugular venous pressure, and radiological signs of congestive HF. Hospitalization was unplanned when an overnight hospital stay was required for major therapeutic intervention or surgery triggered by symptoms or other pathological findings (e.g. laboratory values). Conversely, planned hospitalization was one scheduled for diagnostic or preventive procedures, without symptoms or other pathological findings. Any hospitalization that was scheduled before randomization was defined as "planned".

Death during hospitalization: if death occurred within 24 hours after admission, the primary reason for the serious adverse event (SAE) was labeled as death. If death

occurred >24 hours after admission, the primary label for the SAE was according to the discharge letter.

Appropriate ICD shock: defined as when the spontaneous event that triggered the shock was life-threatening. Appropriate ICD therapy (shock or ATP) was excluded when triggered by slow ventricular tachycardia (VT) or secondary arrhythmias. A life-threatening event was defined at VT associated with syncope and/or in fast VT zone (>200 beats/min). Syncope was defined as a temporary loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery.

Resuscitation: defined as an attempt to maintain or restore life by establishing or maintaining an airway (or both), breathing, and circulation through cardiopulmonary resuscitation (chest compressions with or without ventilations), defibrillation, and other related emergency care techniques. Successful resuscitation was defined for all rhythms as the restoration of a spontaneous perfusing rhythm that resulted in more than an occasional gasp, fleeting palpated pulse, or arterial waveform. An out-of-hospital survived event required sustained return of spontaneous circulation (ROSC, no chest compressions required for 20 consecutive minute and persistent signs of circulation) with spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital. For an inhospital survived event, ROSC for 20 minutes was required (or the return of circulation if extracorporeal circulatory support is applied). Resuscitation of sudden cardiac arrest was counted as cardiovascular death, but with ongoing follow-up.

Cardiovascular death: death was classified as cardiovascular unless an unequivocal non-cardiovascular cause of death was confirmed by the central adjudication

committee. Cardiovascular death includes sudden death, death due to myocardial infarction, heart failure, or stroke; procedure-related death (death during a cardiovascular investigation/procedure/operation); death due to other specified cardiovascular causes; and presumed cardiovascular deaths (e.g. those for which a non-cardiovascular cause had not been clearly established).

Heart transplantation: patients who undergo emergency heart transplantation due to end-stage heart failure were counted as cardiovascular deaths; those who underwent elective heart transplantation were censored 7 days post-transplant.

Respiratory end point definitions

The presence of predominant CSA (AHI ≥15/h, with more than 50% central events and a central AHI ≥10/h) was based on total recording time on polygraphy (PG) or polysomnography (PSG).

Apnea was defined as >90% reduction from baseline in peak amplitude of the signal from nasal cannula and oral thermistor, lasting at least 10 seconds.

Hypopnea was defined as a ≥30% reduction in flow and a ≥3% desaturation from pre-event baseline for more than 10 seconds OR ≥50% reduction in flow from pre-event baseline for ≥10 seconds.

Obstructive versus central hypopneas were determined on the presence/absence of inspiratory flow limitation and/or paradoxical abdominal/thoracic movements on respiratory inductance plethysmography (RIP) if available.

A central apnea was defined in the absence of thoracoabdominal excursions. If the central component of an apnea already satisfied the definition of a central apnea (i.e.

≥10 sec), three consecutive obstructive breaths were needed to classify that as an obstructive apnea. Just one or two obstructed breaths at the end of an apnea didn't change the classification as a central apnea.

The start of the event was marked at the end of the preceding normal breath; the end at the beginning of the first normal breath or breaking breath. On nasal cannula, return to normal corresponded to the occurrence of 2 rounded breaths or of one big breath. On RIP, return to normal corresponded to 2 large breaths or to a very clear change in paradox. The occurrence of EEG arousals and/or desaturation dips was also be used to assert the termination of the respiratory event if available.

For PSG, the number of apnea and hypopnea per hour of sleep (AHI) was determined for total sleep time and then re-calculated for the total recording time.

Cheyne-Stokes respiration was defined as ≥3 episodes of continuous cycles of waxing and waning tidal volumes with periods of hyperventilation separated by central apneas or hypopneas. It was quantified by the presence or absence, and if present by the percentage of the recording time: <20%, ≥20% and <50%, ≥50%.

Oxygen desaturation refers to a ≥3% change in saturation associated with any respiratory event. Its magnitude was be measured from the preceding stable level (during or immediately prior to the hypopnea) and its minimum, which is the nadir level, reached within 30 sec after the termination of the event.

Arousals linked to respiratory events: EEG arousal was scored according to the American Sleep Disorders Association (ASDA) criteria. The arousals were associated with the respiratory event if they begin within 5 seconds before or up to 3 seconds after the termination of the respiratory event.

Statistical analysis

Statistical analysis of secondary end points

Secondary end points were analyzed according to type of scale: time-to-event end points were analyzed as described above by log-rank tests or cause-specific Cox regression models for adjustment of baseline imbalances and without or with interaction terms (subgroup analyses); dichotomous variables (improvement in NYHA class) were analyzed by a likelihood-ratio Chi-square test; continuous end points were analyzed by analysis of covariance (ANCOVA) including the baseline value as a covariate if available; repeated measurements/time courses were analyzed using mixed longitudinal data analysis with robust estimates to minimize potential bias due to differences in follow-up time. All secondary end point comparisons were performed at $\alpha=0.05$ without adjustment for multiplicity.

Post-hoc analyses, deviations of the published analysis from study protocol and statistical analysis plan

The study protocol stated that the primary log-rank test should be performed 'stratified by country as differences in the control event rates of countries have to be expected'. Recruitment was more difficult than expected and therefore the number of participating countries had to be increased in steps. At the end of recruitment some countries had enrolled only a small number of patients, with event counts of zero or slightly above resulting in numeric instability of the pre-defined statistical models. Given that no between-country differences in control group event rates were found, the steering committee decided (on suggestion of the statistician) to remove the stratification requirement.

The study protocol provided two further subordinated primary end points (composite end points with a different mixture of components) which were to be tested at the same type-I error level as the first primary end point, but only if the first primary end point was significant (closed testing procedure). Since this was not the case, the alternative composites are not shown tested hierarchically but tested as if they were secondary end points.

Cumulative incidence curves were presented instead of the Kaplan-Meier curves suggested in the study protocol because competing risks that could bias Kaplan-Meier curves[2] had to be taken into account for most of the event end points (see below). In addition, hazard rates and ratios, as well as cause-specific hazard rates and ratios, were calculated for time-to-event end points without and with competing events, respectively.

Some variables which reflect changes associated with continued use of the ASV device were only available for the ASV group. Within-group comparisons were not specified in the statistical analysis plan. These are presented as comparisons between follow-up measurements and baseline.

Patient withdrawals and follow-up

There were three types of withdrawal specified in the SERVE-HF study protocol:

1. Yearly patient contact by phone and shipping of quality of life and sleepiness questionnaires and contacts to the patient's family doctor accepted;
2. Final contact with patient at study end accepted;
3. No further contact accepted at all.

European Union (EU) data protection rules in the EC Data Protection Directive (Directive 95/46/EC "DPD"), and in its later extension the EC Privacy and Electronic Communications Directive ("PECD"), were strictly followed by all eleven countries participating in SERVE-HF. As a result, level 3 withdrawals were handled as explicitly stated, i.e. no further contact at all, meaning that mortality data were not available. The majority of level 1 and 2 withdrawal patients were successfully contacted for final assessment.

Handling of missing data and competing risks

Missing data in time-to-event end points were handled as censored observations. In the presence of competing events (e.g. cardiovascular mortality), the cause-specific hazards model was applied to calculate cause-specific hazard ratios (HRs). These Cox models are conditional and were chosen since they allow an etiologic interpretation of HRs. In contrast, HRs of a Fine Gray model relate to marginal effects and thus were not used.

In the presence of competing risks, Kaplan-Meier curves are biased[2,3] and thus were replaced by cumulative incidence curves estimated by Aalen-Johansen estimates[4] which specialize to Kaplan-Meier curves if no competing events are present (e.g. primary end point, total mortality).

These methods were applied to the following competing event end points:

- First secondary endpoint: Time to CV death or life-saving CV intervention or unplanned hospitalization for worsening heart failure (competing event: non-CV death)

- Time to CV death (competing event: non-CV death)
- Time to all-cause hospitalization (competing event: all-cause death)
- Time to non-CV death (competing event: CV death)
- Time to individual event types included in the primary end point (unplanned hospitalization for worsening heart failure, heart transplantation, appropriate shock from ICD, long-term ventricular assist device (LTVAD) implantation, survived resuscitation, and survived resuscitation of sudden cardiac arrest; competing event: all-cause death)

Missing data were not imputed. According to the Statistical Analysis Plan (SAP), available data was used. For the analysis of longitudinal data a full-information maximum likelihood estimation (random effects model with repeated measurements) was applied. Assuming MAR (missing at random) this method can handle missing data in the dependent variable and yields less biased estimators than LOCF (last observation carried forward).[5] With respect to use data, at each follow-up, the average (over days) use since the last reading of device data was assessed in the ASV group. Missing data were treated as missing. If device was not used, zeros were entered for this patient and included in the calculation of the within-group averages (over patients).

Mask use

The type of mask selected at baseline for delivery of ASV was a nasal mask in 101 patients (15.2%) and a full face mask in 505 patients (75.8%); choice of initial mask was unknown in 60 patients allocated to ASV (9%).

Sensitivity analyses for all-cause and cardiovascular mortality

Adjusted endpoint analyses were conducted for the primary end point, all-cause mortality and cardiovascular mortality (Figure S1) in order to account for the imbalance in the prescription of antiarrhythmics; this showed that baseline between-group differences did not influence the study results.

Differences in all-cause and cardiovascular mortality remained significantly different between the ASV and control groups in a robustness analysis performed to define the effect of censoring life-saving cardiovascular interventions (Tables S5 & S6).

Heart transplant (HTx), long-term ventricular assist device (LTVAD) and shock

Patients with HTx, LTVAD, or (appropriate) shock were censored at their respective event time. Given that all of these events contribute to the primary end point, this additional analysis was only performed for the all-cause mortality and cardiovascular mortality end points. The number of events ignored for each of these end points was 69/425 and 61/357, respectively. The resulting analysis is shown in Table S5.

Heart transplant (HTx), long-term ventricular assist device (LTVAD), shock and resuscitation

Including resuscitation as an additional life-saving event, the number of events ignored for the two end points was 90/425 and 81/357, respectively. The resulting analysis is shown in Table S6.

Supplementary Tables

Table S1. Country of Enrolment for Study Patients.

Characteristic	Control (n=659)	ASV (n=666)
Country – no. (%)		
Germany	459/659 (69.7)	467/666 (70.1)
France	123/659 (18.7)	119/666 (17.9)
Sweden	19/659 (2.9)	20/666 (3.0)
United Kingdom	19/659 (2.9)	18/666 (2.7)
Australia	13/659 (2.0)	16/666 (2.4)
Denmark	12/659 (1.8)	12/666 (1.8)
Norway	5/659 (0.8)	5/666 (0.8)
Czech Republic	4/659 (0.6)	3/666 (0.5)
Finland	3/659 (0.5)	4/666 (0.6)
Switzerland	1/659 (0.2)	2/666 (0.3)
Netherlands	1/659 (0.2)	0

Table S2. Device data during adaptive servo-ventilation therapy

	First ASV night	3 months	12 months	24 months	36 months	48 months
IPAP – cmH_2O						
Median	9.7 (5.4, 17.0)	9.6 (6.3, 17.0)	9.8 (7.0, 17.5)	9.9* (7.0, 16.8)	10.1* (7.3, 16.9)	10.1* (7.3, 15.6)
95th percentile	14.1 (7.0, 22.10)	13.7* (6.6, 21.6)	13.9§ (7.2, 21.2)	13.9 (9.4, 20.9)	13.8 (8.4, 20.9)	13.7§ (10.2, 20.0)
EPAP – cmH_2O						
Median	5.5 (3.0, 11.0)	5.5 (3.0, 11.0)	5.7‡ (3.0, 12.0)	5.8* (4.0, 11.0)	6.0* (4.0, 11.0)	6.1* (4.0, 11.0)
95th percentile	5.6 (4.0, 11.0)	5.6 (4.0, 14.8)	5.7 (3.0, 12.2)	5.8¶ (4.0, 12.0)	6.1* (4.0, 12.0)	6.1* (4.0, 11.0)
RR – /min						
Median	16.0 (11.0, 31.0)	16.4* (12.0, 26.0)	16.4* (12.0, 26.0)	16.5* (12.0, 27.0)	16.6* (13.0, 27.0)	16.9* (14.0, 24.0)
95th percentile	20.0 (8.6, 40.0)	19.7† (6.9, 37.0)	19.8 (12.0, 36.0)	19.9 (15.0, 38.0)	19.9 (15.0, 32.0)	20.2 (16.0, 36.0)
Leak – L/min						
Median	4.8 (0.0, 83.0)	4.6 (0.0, 121.2)	4.2 (0.0, 83.0)	4.4 (0.0, 60.0)	4.9 (0.0, 101.0)	3.6 (0.0, 62.0)
95th percentile	21.7 (0.0, 195.6)	16.9* (0.0, 138.0)	16.2* (0.0, 120.0)	17.9** (0.0, 120.0)	18.8 (0.0, 120.0)	16.1‡‡ (0.0, 120.0)

Table shows mean within-ASV-group values at baseline (first ASV night) and follow-up with range and P-values that are derived from a statistical model with change from baseline as response, patients as random effect, visits as repeated measurements with 1st-order autocorrelation structure.
For comparisons with baseline: *P<0.001, †P=0.02, ‡P=0.002, §P=0.03, ¶P=0.006, **P=0.009, ‡‡P=0.004.
ASV, adaptive servo-ventilation; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; RR, respiratory rate.

Table S3. Average adaptive servo-ventilation device usage over time

	Proportion of patients with average nightly usage – %						Average usage (h/night)
	<1 h	**1–2 h**	**2–3 h**	**3–4 h**	**4–5 h**	**≥ 5 h**	
Follow-up							
2 weeks	16.8	6.8	6.8	10.5	12.4	46.8	4.1
3 months	21.7	6.5	8.0	8.8	11.1	43.9	3.9
12 months	29.4	7.3	7.9	7.7	9.4	38.3	3.4
24 months	31.4	7.2	4.9	5.4	11.4	39.8	3.5
36 months	40.1	6.6	3.9	6.6	6.2	36.6	3.2
48 months	38.6	5.9	5.9	5.9	8.5	35.3	3.2
60 months	33.3	2.8	5.6	6.9	11.1	40.3	3.7
Total	26.7	6.7	6.6	8.0	10.5	41.5	3.7

Table S4. Respiratory effects of adaptive servo-ventilation therapy

	Baseline	3 months	12 months	24 months	36 months	48 months
AHI – /h	31.2 (10.3, 115.3)	6.7* (0.0, 71.9)	6.6* (0.0, 50.8)	6.2* (0.0, 46.4)	6.5* (0.0, 61.2)	6.8* (0.0, 37.7)
cAHI – /h	25.2 (0.0, 89.6)	4.0* (0.0, 54.4)	4.0* (0.0, 48.0)	3.2* (0.0, 46.4)	3.3* (0.0, 36.5)	3.2* (0.0, 32.2)
cAHI/total AHI – %	80.8 (0.0, 100.0)	53.3* (0.0, 100.0)	48.9* (0.0, 100.0)	40.4* (0.0, 100.0)	42.6* (0.0, 100.0)	39.7* (0.0, 100.0)
cAI/total AHI – %	44.6 (0.0, 100.0)	12.1* (0.0, 100.0)	12.8* (0.0, 100.0)	12.8* (0.0, 100.0)	14.3* (0.0, 100.0)	13.4* (0.0, 100.0)
ODI – /h	32.1 (0.0, 157.5)	8.9* (0.0, 78.5)	8.6* (0.0, 68.0)	9.2* (0.0, 66.3)	8.9* (0.0, 59.0)	9.9* (0.0, 66.3)
Minimum SaO_2 – %	80.7 (43.0, 93.0)	86.0* (50.0, 100.0)	85.5* (40.0, 100.0)	86.7* (72.0, 97.0)	86.3* (70.0, 97.0)	86.0* (67.0, 97.0)
Mean SaO_2 – %	92.8 (78.0, 99.0)	93.8* (84.0, 100.0)	93.7* (87.0, 100.0)	93.8* (88.3, 98.2)	93.7* (88.0, 97.8)	93.5* (88.9, 99.0)
Time with SaO_2 <90% – min	50.7 (0.0, 458.6)	19.2* (0.0, 344.0)	19.9* (0.0, 268.6)	18.0* (0.0, 284.8)	18.8* (0.0, 291.0)	24.6* (0.0, 278.0)

Table shows mean within-ASV-group values at baseline (first ASV night) and follow-up with range and P-values that are derived from a statistical model with change from baseline as response, patients as random effect, visits as repeated measurements with 1st-order autocorrelation structure.

*P<0.001 compared with baseline.

AHI, apnea-hypopnea index (calculated over the total recording time); cAI, central apnea index; cAHI, central apnea-hypopnea index; ODI, oxygen saturation index; SaO_2, oxygen saturation.

Table S5. Sensitivity analysis (censoring at HTx, LTVAD or shock)

	Control (n=659)		ASV (n=666)			
	n (%)	Incidence/year (95% CI)	n (%)	Incidence/year (95% CI)	HR (95% CI)	P-value
End point (without prior life-saving CV intervention)						
All-cause mortality	161 (24.4)	0.084 (0.072, 0.098)	195 (29.3)	0.105 (0.090, 0.120)	1.25 (1.01, 1.54)	0.04
CV death	131 (19.9)	0.068 (0.057, 0.081)	165 (24.8)	0.088 (0.075, 0.103)	1.30 (1.03, 1.63)	0.03

ASV, adaptive servo-ventilation; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; HTx, heart transplantation; LTVAD, long-term ventricular assist device.

Table S6. Sensitivity analysis (censoring at HTx, LTVAD, shock or resuscitation)

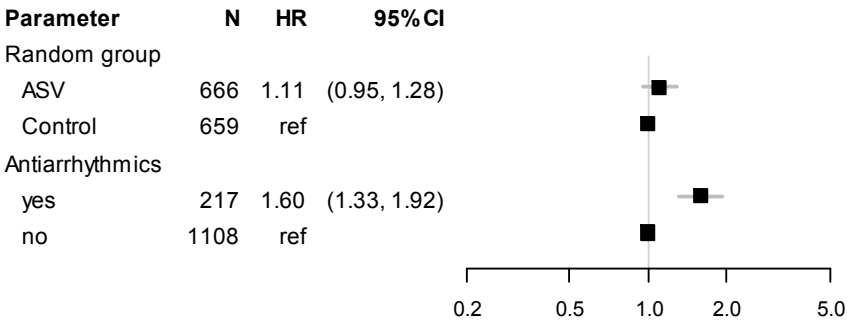
	Control (n=659)		ASV (n=666)			
	n (%)	Incidence/year (95% CI)	n (%)	Incidence/year (95% CI)	HR (95% CI)	P-value
End point (without prior life-saving CV intervention)						
All-cause mortality	152 (23.1)	0.080 (0.067, 0.093)	183 (27.5)	0.099 (0.085, 0.114)	1.25 (1.01, 1.55)	0.04
CV death	123 (18.7)	0.064 (0.053, 0.077)	153 (23.0)	0.083 (0.070, 0.097)	1.29 (1.02, 1.63)	0.04

ASV, adaptive servo-ventilation; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; HTx, heart transplantation; LTVAD, long-term ventricular assist device.

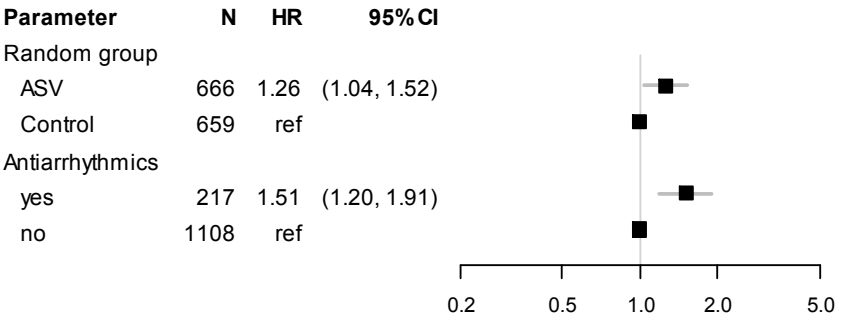
Supplementary Figures

Figure S1. Forest plot of Cox regression models of ASV vs. control with statistical control of antiarrhythmics as additional factors which wase not balanced at baseline for the primary end point (all-cause death or life-saving cardiovascular intervention plus unplanned hospitalization for worsening chronic heart failure) (A), all-cause mortality (B) and cardiovascular mortality (C). The bars represent 95% confidence intervals. CI, confidence interval; HR, hazard ratio.

A.



B.


Parameter N HR 95% CI
Random group
ASV 666 1.26 (1.04, 1.52)
Control 659 ref
Antiarrhythmics
yes 217 1.51 (1.20, 1.91)
no 1108 ref
0.2
0.5
1.0
2.0
5.0

C.

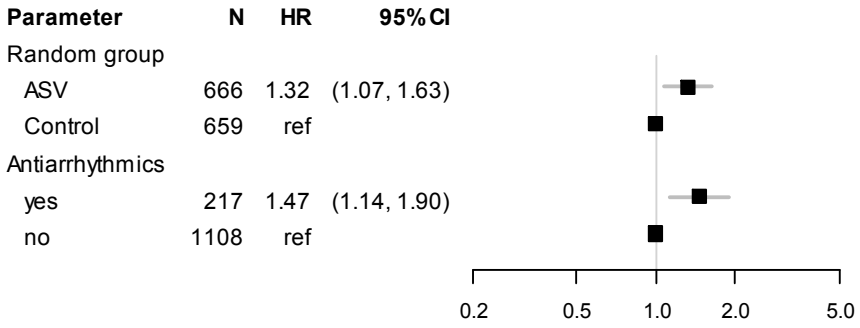
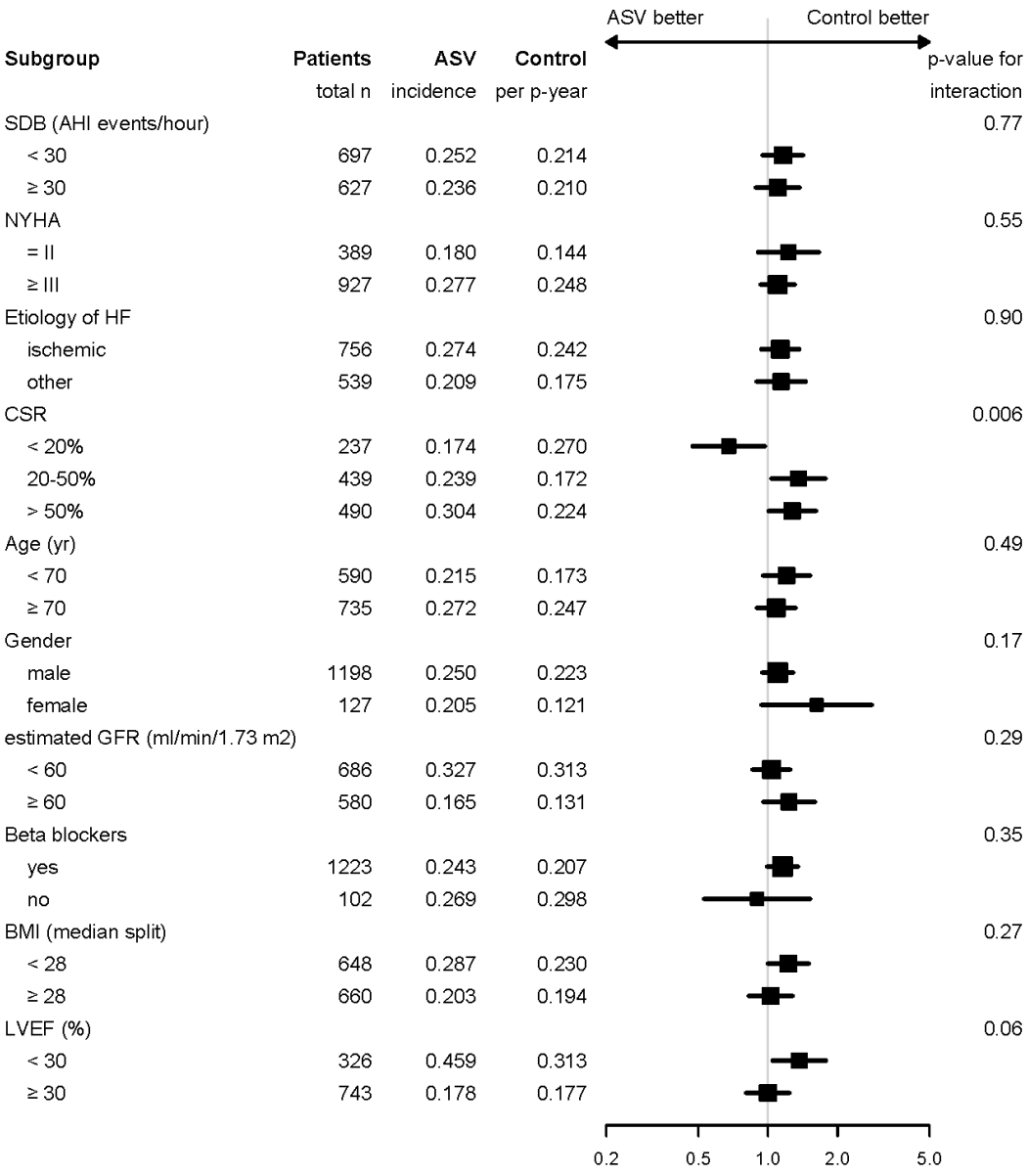

Parameter N HR 95% CI
Random group
ASV 666 1.32 (1.07, 1.63)
Control 659 ref
Antiarrhythmics
yes 217 1.47 (1.14, 1.90)
no 1108 ref
0.2
0.5
1.0
2.0
5.0

Figure S2. Risk of the primary end point (all-cause death or life-saving cardiovascular intervention plus unplanned hospitalization for worsening chronic heart failure) (A) and cardiovascular mortality (B) in patient subgroups of the control and ASV groups. The bars represent 95% confidence intervals. BMI, body mass index; CSR, Cheyne-Stokes respiration; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SDB, sleep-disordered breathing.

A.



Subgroup	Patients total n	ASV incidence	Control per p-year	p-value for interaction
SDB (AHI events/hour)				0.77
< 30	697	0.252	0.214	
≥ 30	627	0.236	0.210	
NYHA				0.55
= II	389	0.180	0.144	
≥ III	927	0.277	0.248	
Etiology of HF				0.90
ischemic	756	0.274	0.242	
other	539	0.209	0.175	
CSR				0.006
< 20%	237	0.174	0.270	
20-50%	439	0.239	0.172	
> 50%	490	0.304	0.224	
Age (yr)				0.49
< 70	590	0.215	0.173	
≥ 70	735	0.272	0.247	
Gender				0.17
male	1198	0.250	0.223	
female	127	0.205	0.121	
estimated GFR (ml/min/1.73 m2)				0.29
< 60	686	0.327	0.313	
≥ 60	580	0.165	0.131	
Beta blockers				0.35
yes	1223	0.243	0.207	
no	102	0.269	0.298	
BMI (median split)				0.27
< 28	648	0.287	0.230	
≥ 28	660	0.203	0.194	
LVEF (%)				0.06
< 30	326	0.459	0.313	
≥ 30	743	0.178	0.177	

B.

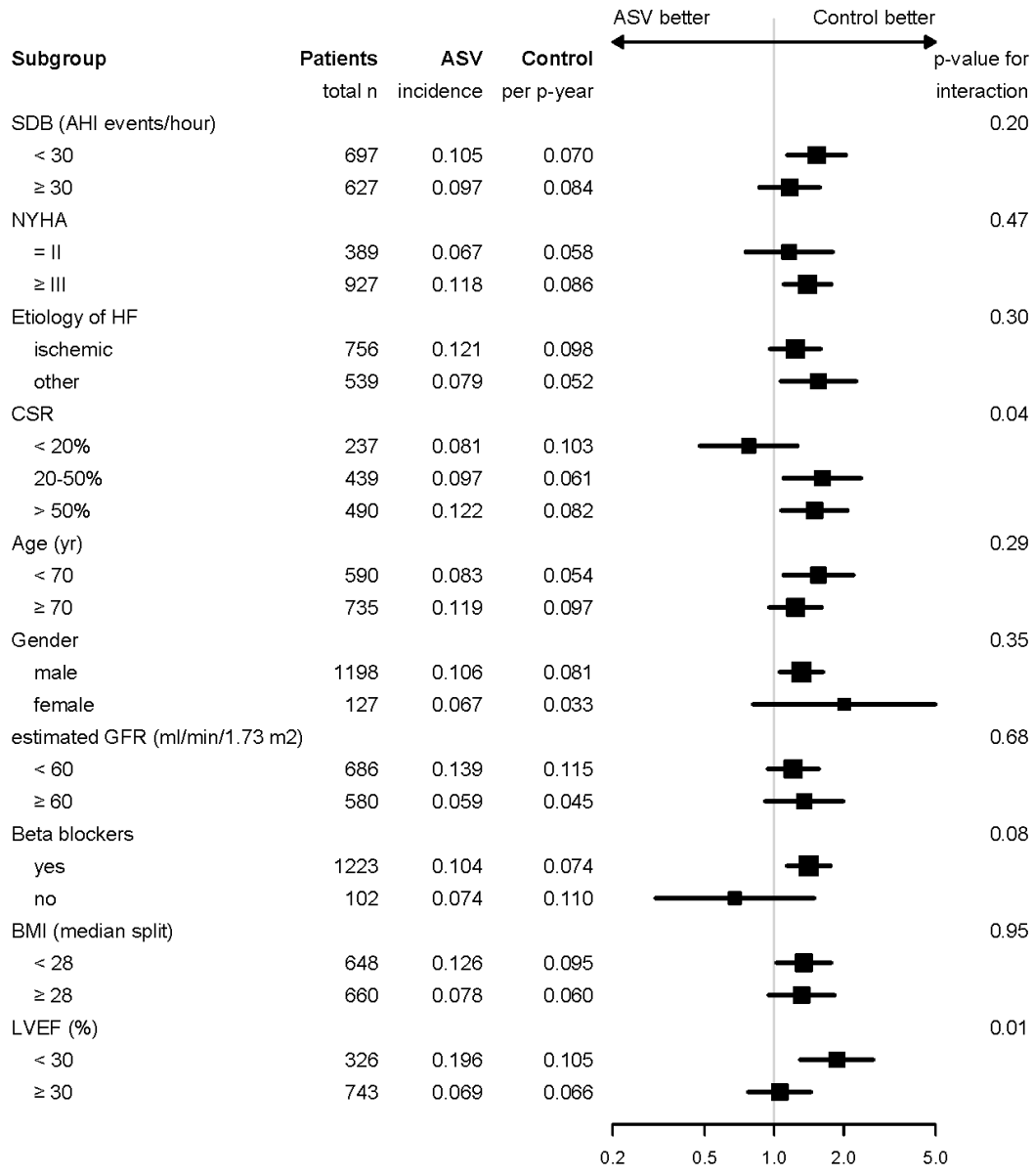
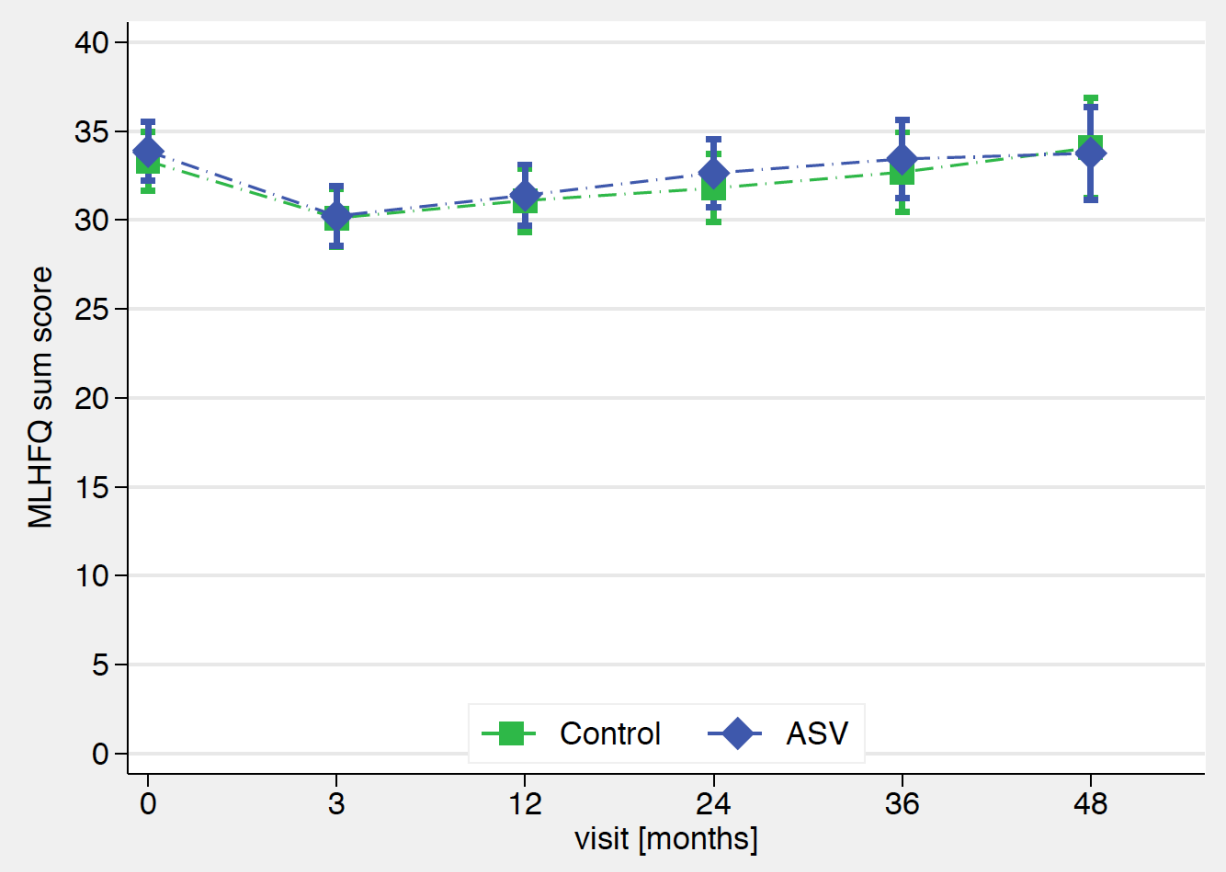

ASV better
Control better
Subgroup
Patients total n
ASV incidence
Control per p-year
p-value for interaction
SDB (AHI events/hour) 0.20
< 30 697 0.105 0.070
≥ 30 627 0.097 0.084
NYHA 0.47
= II 389 0.067 0.058
≥ III 927 0.118 0.086
Etiology of HF 0.30
ischemic 756 0.121 0.098
other 539 0.079 0.052
CSR 0.04
< 20% 237 0.081 0.103
20-50% 439 0.097 0.061
> 50% 490 0.122 0.082
Age (yr) 0.29
< 70 590 0.083 0.054
≥ 70 735 0.119 0.097
Gender 0.35
male 1198 0.106 0.081
female 127 0.067 0.033
estimated GFR (ml/min/1.73 m2) 0.68
< 60 686 0.139 0.115
≥ 60 580 0.059 0.045
Beta blockers 0.08
yes 1223 0.104 0.074
no 102 0.074 0.110
BMI (median split) 0.95
< 28 648 0.126 0.095
≥ 28 660 0.078 0.060
LVEF (%) 0.01
< 30 326 0.196 0.105
≥ 30 743 0.069 0.066
0.2
0.5
1.0
2.0
5.0

Figure S3. Disease-specific quality of life: Minnesota Living with Heart Failure Questionnaire (MLHFQ). The **A** panel shows average follow-up values in the control and adaptive servo-ventilation (ASV) groups derived from a random effects model with repeated measurements. The **B** panel shows mean changes from baseline and p-values derived from a statistical model with change from baseline as response, patients as random effect, visits as repeated measurements with first-order autocorrelation structure, baseline as covariate and random group as factor. P(level, ASV vs. control) compares the average levels between groups. P(trend) is for the results of the test of the first-order polynomial contrast for the pooled sample vs. zero. P(trend; ASV vs. Control) compares the trends between the two treatment groups. Since P(trend, ASV vs Control) ≥0.05 the individual trends of the respective groups are not reported. Plots show adjusted means and 95% confidence intervals.

A.



B.

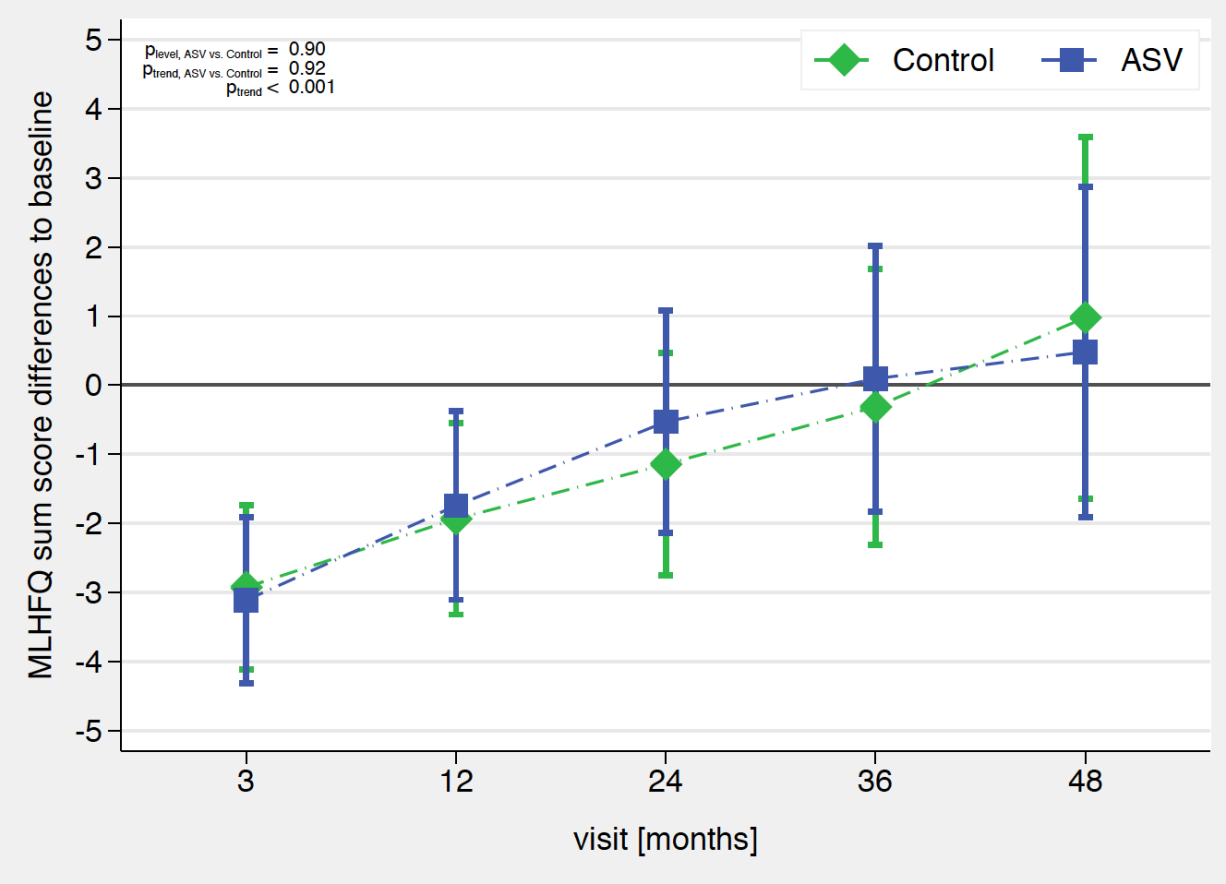
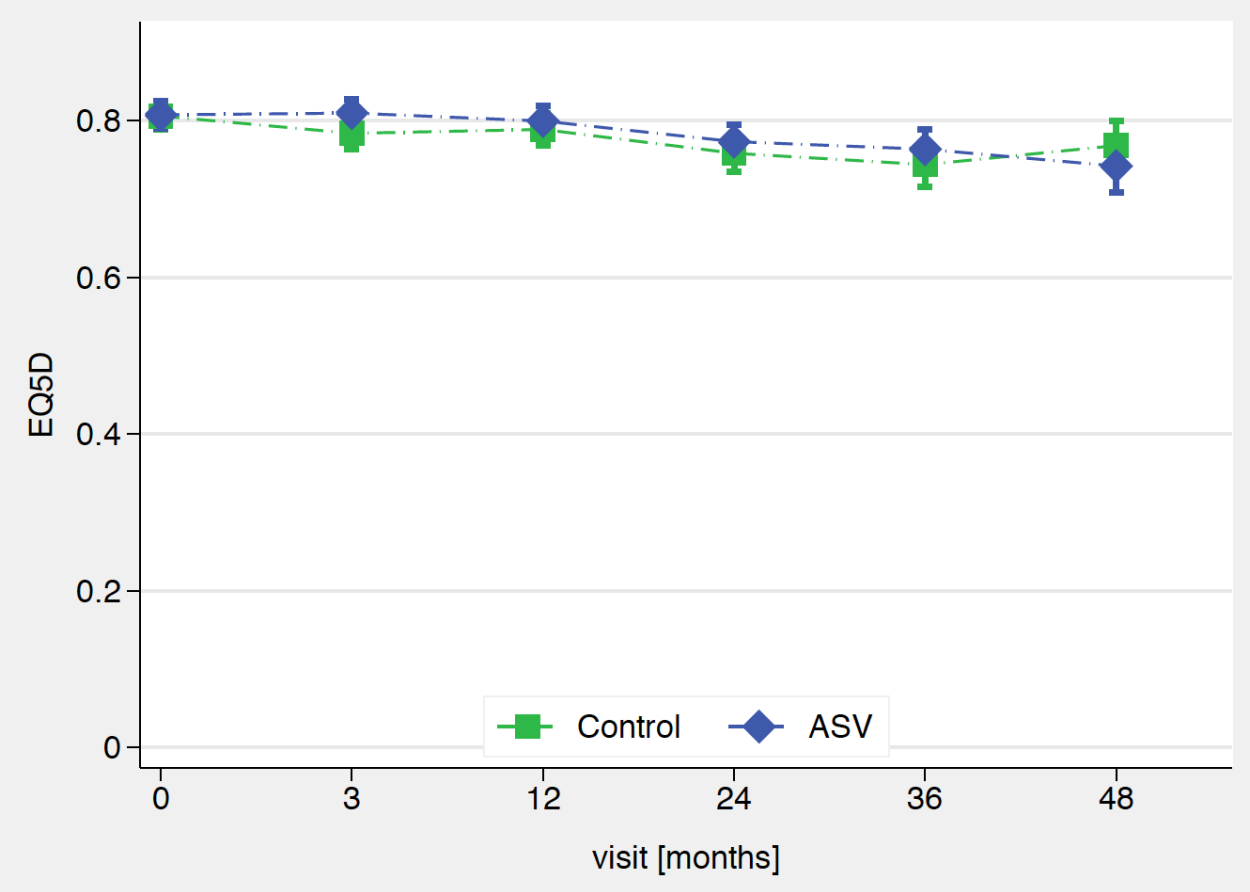

$p_{level,\ ASV\ vs.\ Control}$ = 0.90
$p_{trend,\ ASV\ vs.\ Control}$ = 0.92
p_{trend} < 0.001
Control
ASV
MLHFQ sum score differences to baseline
5
4
3
2
1
0
-1
-2
-3
-4
-5
3
12
24
36
48
visit [months]

Figure S4. General quality of life: EuroQol 5D (EQ5D). The **A** panel shows average follow-up values in the control and adaptive servo-ventilation (ASV) groups derived from a random effects model with repeated measurements. The **B** panel shows mean changes from baseline and p-values derived from a statistical model with change from baseline as response, patients as random effect, visits as repeated measurements with first-order autocorrelation structure, baseline as covariate and random group as factor. P(level, ASV vs. control) compares the average levels between groups. P(trend) is for the results of the test of the first-order polynomial contrast for the pooled sample vs. zero. P(trend; ASV vs. Control) compares the trends between the two treatment groups. Since P(trend, ASV vs Control) ≥0.05 the individual trends of the respective groups are not reported. Plots show adjusted means and 95% confidence intervals.

A.



B.

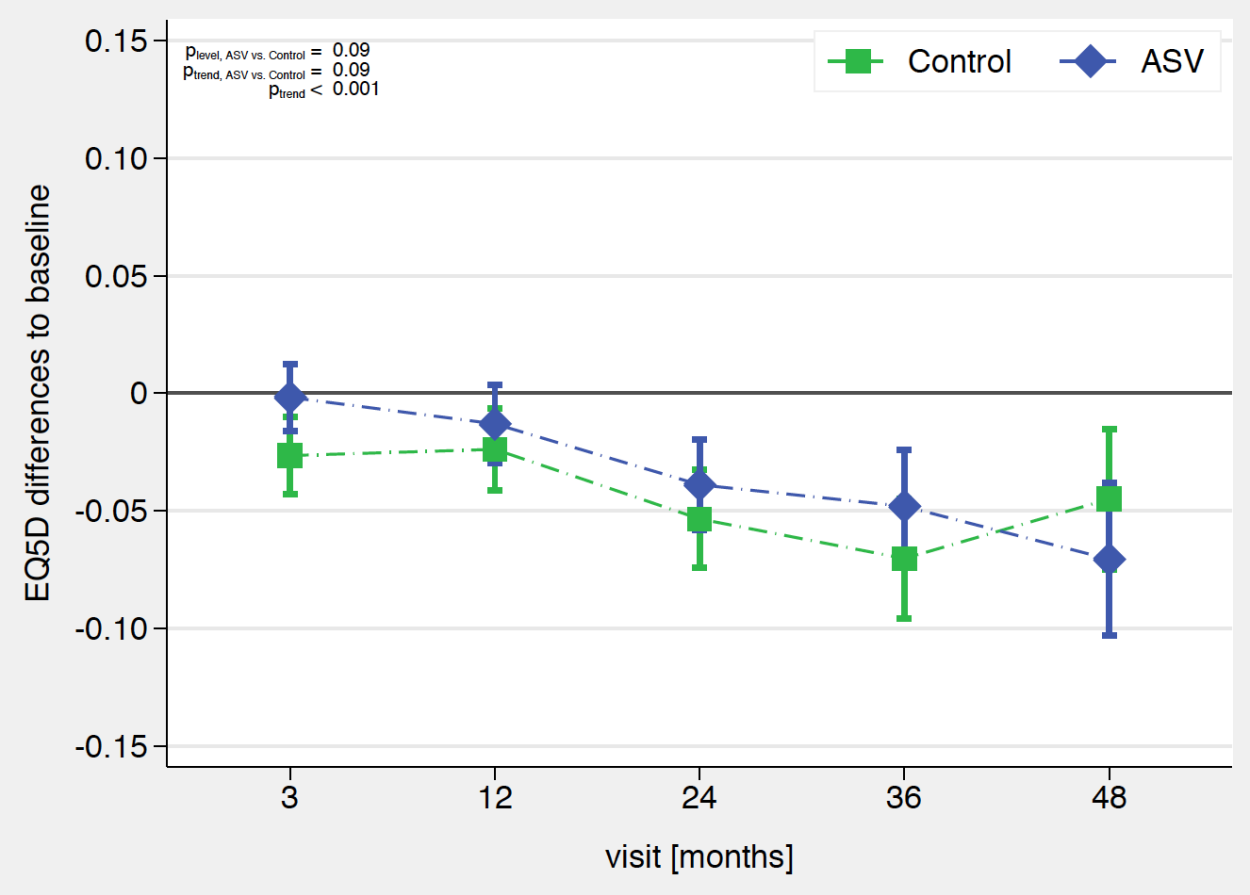
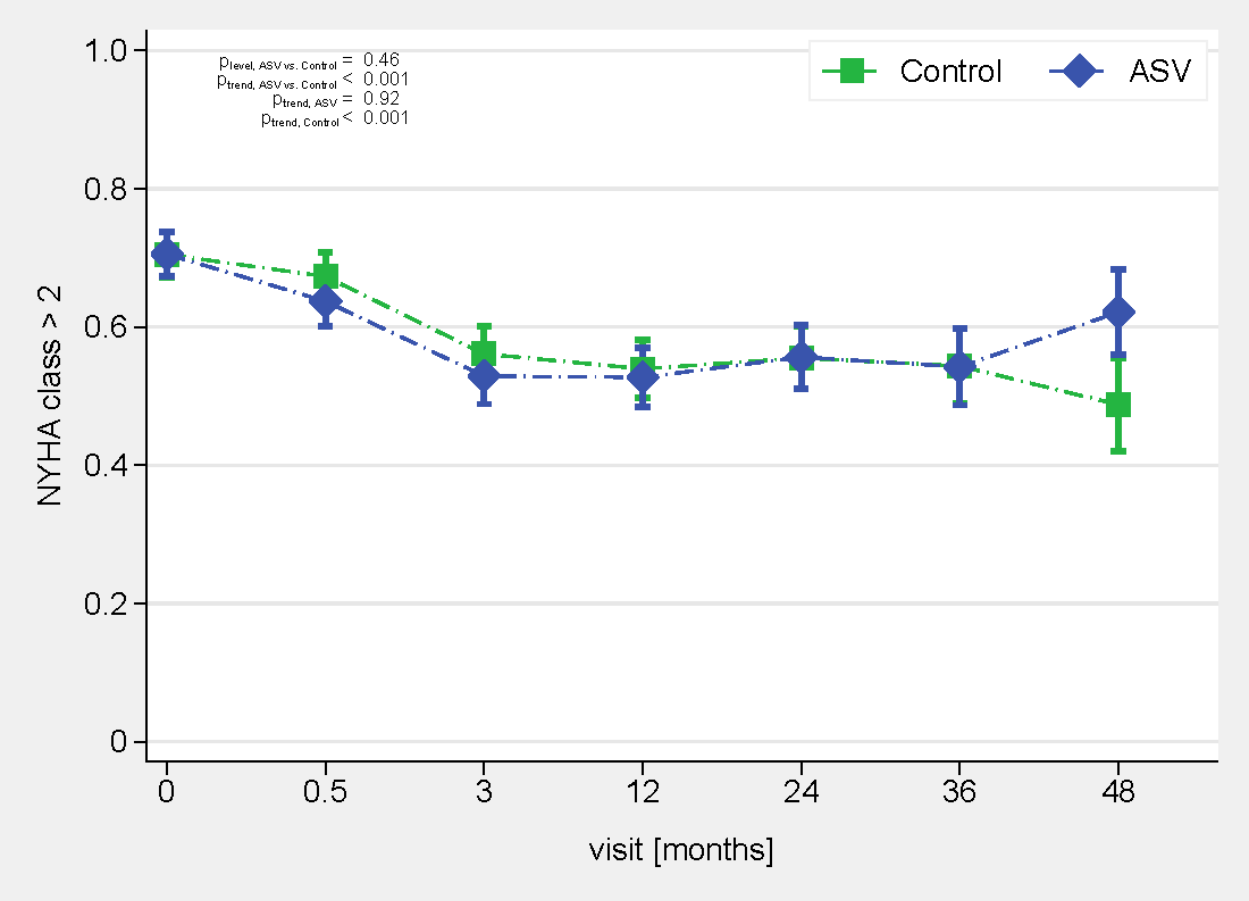

$p_{level,\ ASV\ vs.\ Control}$ = 0.09
$p_{trend,\ ASV\ vs.\ Control}$ = 0.09
p_{trend} < 0.001
Control
ASV
0.15
0.10
0.05
0
-0.05
-0.10
-0.15
EQ5D differences to baseline
3
12
24
36
48
visit [months]

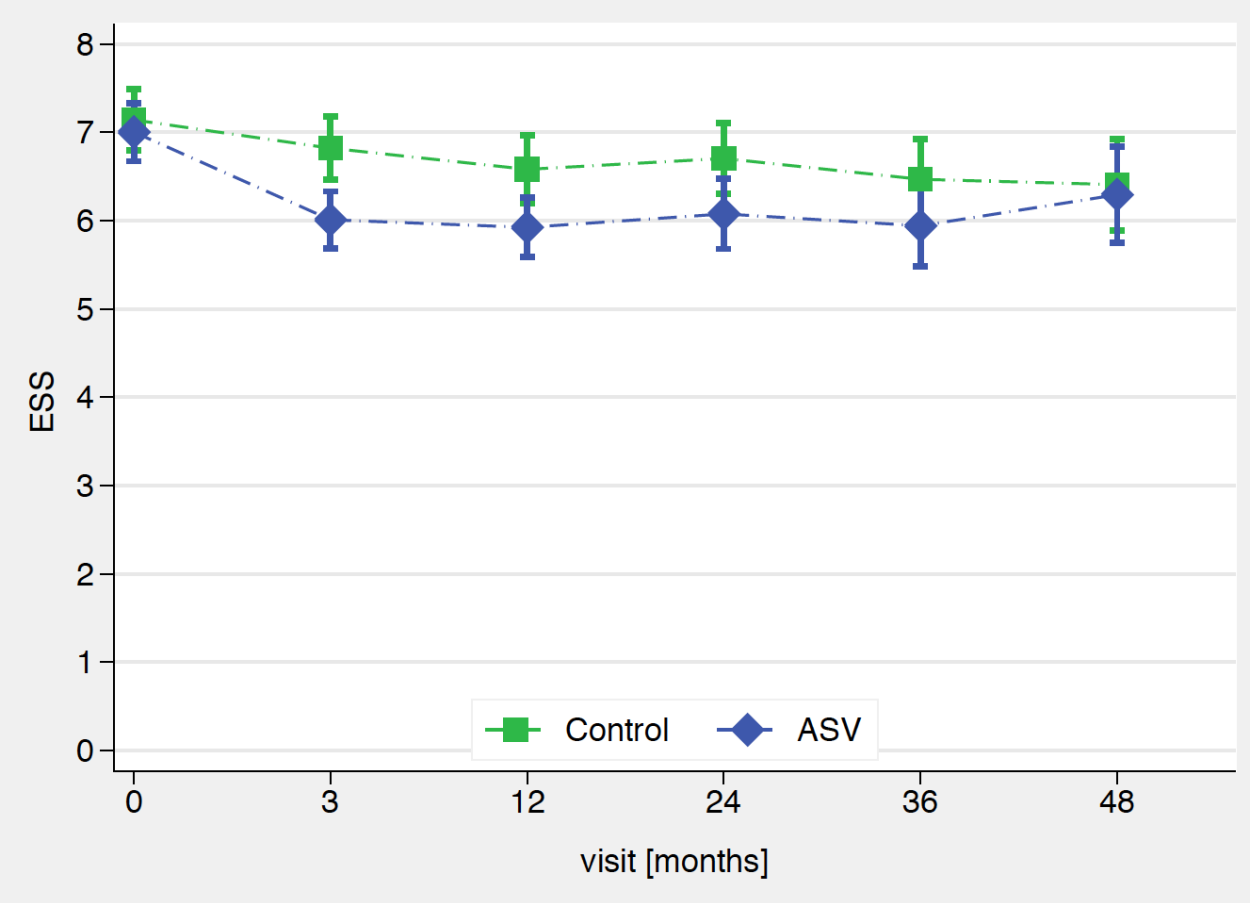
Figure S5. Proportion of patients in NYHA class >2 in the control and Adaptive Servo-Ventilation (ASV) groups. For dichotomous endpoints, mean and p-values are derived from a random effects logistic regression model with the endpoint as response, patients as random effect, visits as repeated measurements, baseline as covariate and random group as factor where applicable. P(level, ASV vs. Control) compares the average levels between groups. P(trend, Control) and P(trend, ASV) result of the test of the 1st-order polynomial contrast of the respective random group sample vs. zero. P(trend; ASV vs. Control) compares the trends between treatment groups.



1.

Figure S6. Epworth Sleepiness Scale (ESS) score. The **A** panel shows average follow-up values in the control and adaptive servo-ventilation (ASV) groups derived from a random effects model with repeated measurements. The **B** panel shows mean changes from baseline and p-values derived from a statistical model with change from baseline as response, patients as random effect, visits as repeated measurements with first-order autocorrelation structure, baseline as covariate and random group as factor. P(level, ASV vs. control) compares the average levels between groups. P(trend) is for the results of the test of the first-order polynomial contrast for the pooled sample vs. zero. P(trend; ASV vs. Control) compares the trends between the two treatment groups. Since P(trend, ASV vs Control) ≥0.05 the individual trends of the respective groups are not reported. Plots show adjusted means and 95% confidence intervals.

A.



B.

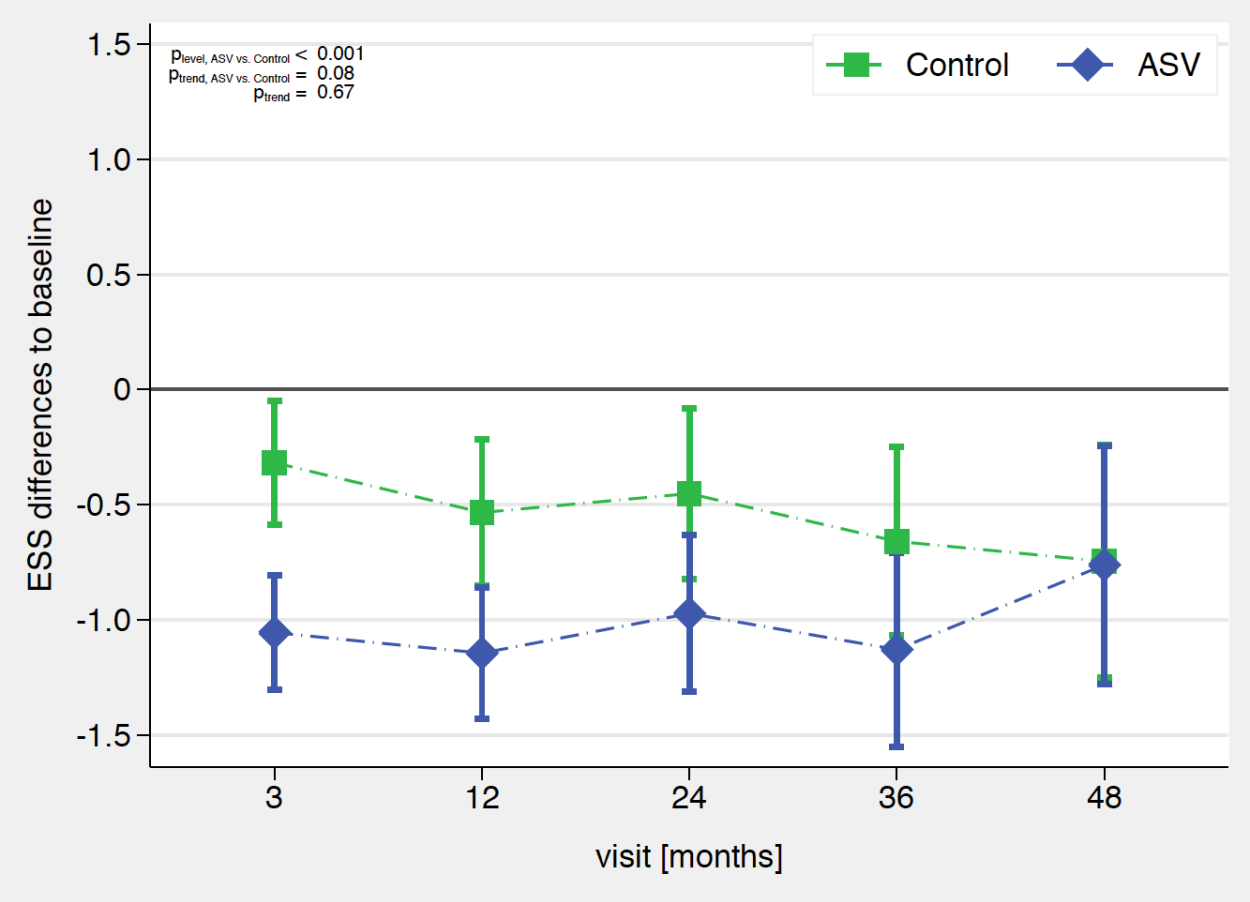
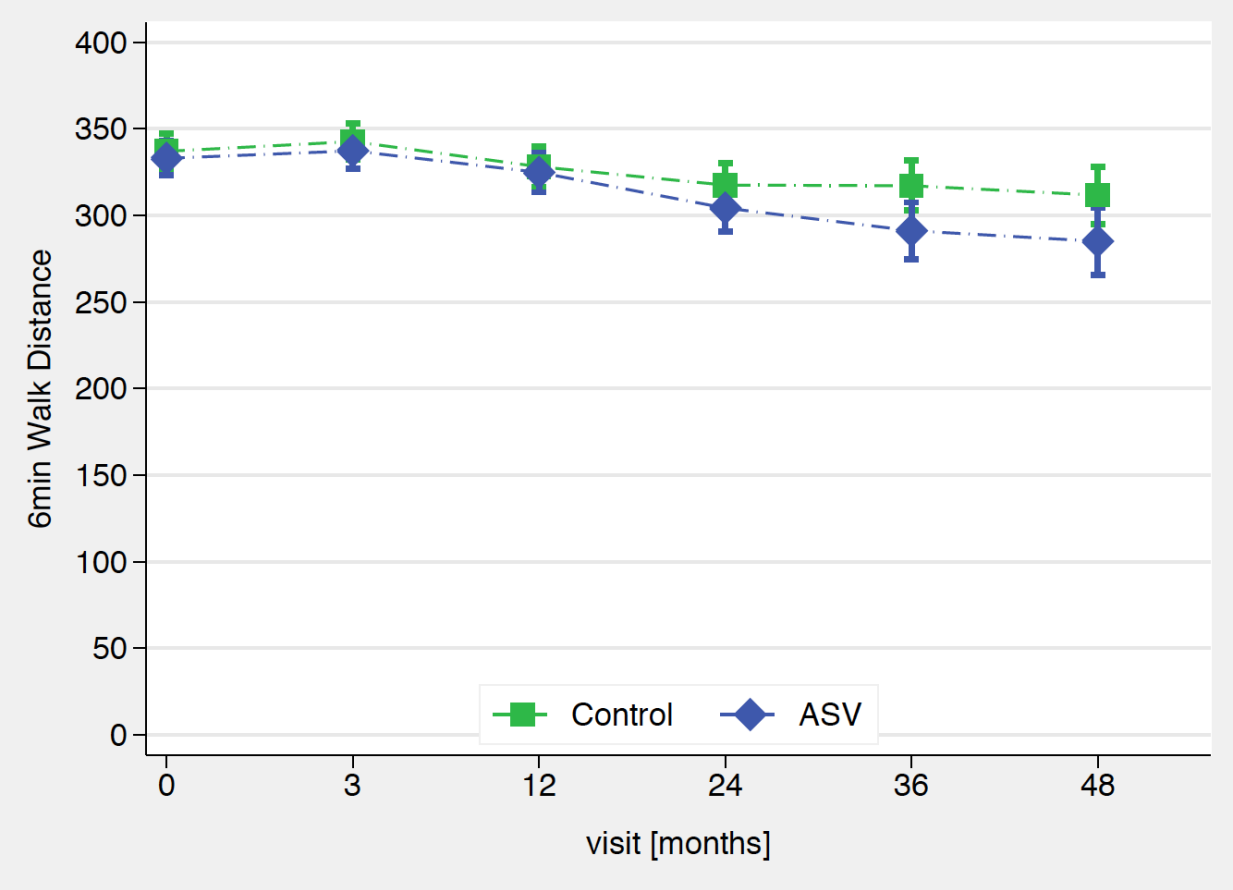
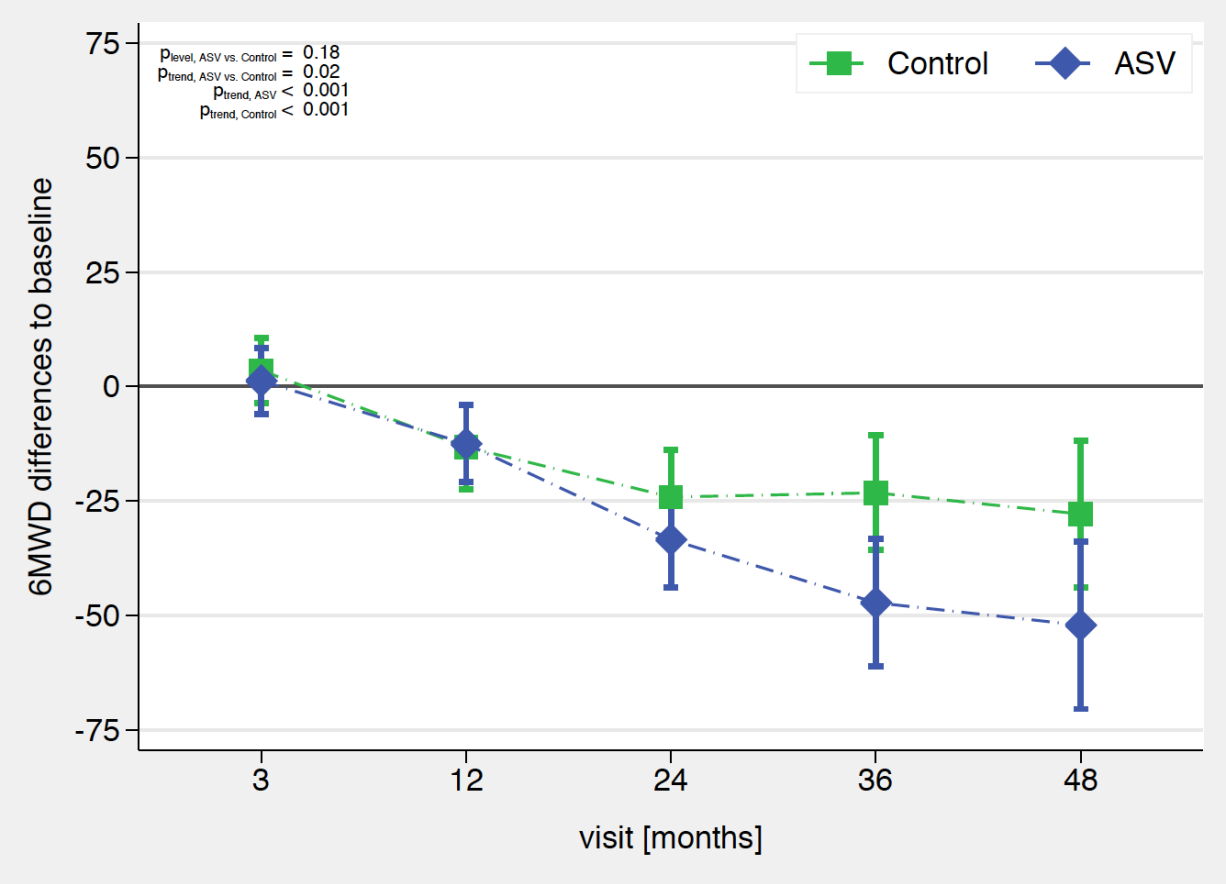

$p_{level,\ ASV\ vs.\ Control}$ < 0.001
$p_{trend,\ ASV\ vs.\ Control}$ = 0.08
p_{trend} = 0.67
Control
ASV
ESS differences to baseline
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
3
12
24
36
48
visit [months]

Figure S7. Six-minute walk distance (6MWD). The **A** panel shows average follow-up values in the control and adaptive servo-ventilation (ASV) groups derived from a random effects model with repeated measurements. The **B** panel shows mean changes from baseline and p-values derived from a statistical model with change from baseline as response, patients as random effect, visits as repeated measurements with first-order autocorrelation structure, baseline as covariate and random group as factor. P(level, ASV vs. control) compares the average levels between groups. P(trend) is for the results of the test of the first-order polynomial contrast for the pooled sample vs. zero. P(trend; ASV vs. Control) compares the trends between the two treatment groups. Since P(trend, ASV vs Control) <0.05 the P values of the individual trends of the respective groups are reported instead of P(trend). P(trend, Control) and P(trend, ASV) result of the test of the first-order polynomial contrast of the respective random group vs. zero. Plots show adjusted means and 95% confidence intervals.

A.



B.


$p_{level,\ ASV\ vs.\ Control} = 0.18$
$p_{trend,\ ASV\ vs.\ Control} = 0.02$
$p_{trend,\ ASV} < 0.001$
$p_{trend,\ Control} < 0.001$
Control
ASV
6MWD differences to baseline
75
50
25
0
-25
-50
-75
3
12
24
36
48
visit [months]

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